

ARTICLE

Legal approaches regarding health-care decisions involving minors: implications for next-generation sequencing

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The development of next-generation sequencing (NGS) technologies are revolutionizing medical practice, facilitating more accurate, sophisticated and cost-effective genetic testing. NGS is already being implemented in the clinic assisting diagnosis and management of disorders with a strong heritable component. Although considerable attention has been paid to issues regarding return of incidental or secondary findings, matters of consent are less well explored. This is particularly important for the use of NGS in minors. Recent guidelines addressing genomic testing and screening of children and adolescents have suggested that as ‘young children’ lack decision-making capacity, decisions about testing must be conducted by a surrogate, namely their parents. This prompts consideration of the age at which minors can provide lawful consent to health-care interventions, and consequently NGS performed for diagnostic purposes. Here, we describe the existing legal approaches regarding the rights of minors to consent to health-care interventions, including how laws in the 28 Member States of the European Union and in Canada consider competent minors, and then apply this to the context of NGS. There is considerable variation in the rights afforded to minors across countries. Many legal systems determine that minors would be allowed, or may even be required, to make decisions about interventions such as NGS. However, minors are often considered as one single homogeneous population who always require parental consent, rather than recognizing there are different categories of ‘minors’ and that capacity to consent or to be involved in discussions and decision-making process is a spectrum rather than a hurdle. *European Journal of Human Genetics* advance online publication, 15 June 2016; doi:10.1038/ejhg.2016.61

INTRODUCTION

The rapid development of next-generation sequencing (NGS) technologies (ie, new high-throughput and massively parallel DNA sequencing) has substantially reduced both the cost and the time required to sequence an entire human genome or exome. This development is likely to change the current practice of medicine by facilitating more accurate, sophisticated and cost-effective genetic testing.¹ Implementation of NGS is already aiding the diagnosis and management of disorders that have a strong heritable component, such as rare diseases,² cardiological conditions³ and cancers.⁴ In addition, NGS is predicted to greatly increase personalized medicine possibilities in the future, including diagnosis of complex disorders, drug therapies and treatments.

This technological development is likely to be particularly relevant for rare diseases in the pediatric population. The low prevalence worldwide makes diagnosis of these rare diseases extremely challenging for clinicians, and let alone for scientific researchers to determine their etiology. Children with rare diseases have a high mortality and morbidity rate, with 30% dying in the first year of life.⁵ Although a rare disease may only affect a small number of children, when pooled, rare diseases represent a significant burden to the health-care system. Therefore, early diagnosis and swift access to appropriate treatment are of key importance for both the families and the medical system

overall. Implementation of NGS in routine diagnostics would help diagnose pediatric conditions of presumed genetic origin more rapidly and more efficiently,^{6–8} and greatly increase the overall diagnostic yield.^{9,10}

Yet, the large amount of information that is generated about a patient through the use of NGS has led technology users, medical professionals, ethicists and other stakeholders to question what kind of information should be returned to the families. NGS generates a wide range of results: some are validated and clinically useful; others are validated, but not associated with any known treatment or preventive measure; and finally, others are of unclear or unknown significance. NGS may also identify incidental findings or mutations that are linked to conditions unrelated to the original diagnostic question. These findings may identify a range of unexpected information, such as the patient’s susceptibility to develop diseases, their ability to respond to different treatments or their carrier status for a recessive disease. This information may be of interest to the patients for their own health or future reproductive choices or alternatively to other family members.

Determining which results and incidental findings should be returned following NGS for diagnostic purposes in minors poses additional challenges. The status of minors requires that a parent or the legal guardian be the primary decision maker. Deciding on behalf of children which incidental findings should (or should not) be

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communicated to the family removes the child's opportunity to be able to make an informed choice about which genetic information he or she wants to know (or not to know), once they develop the capacity to do so. As results will usually be returned to the child's parents, this question also leads to debates about the responsible management of the pre- and post-test counseling processes, and the impact of the information on the parents, the children and the family as a whole.

NGS has the potential to incidentally identify information about one's genetic risk for late-onset conditions, some of which may be without prevention or treatment options.^{11–14} Although this information may not be immediately relevant to the health of the child, it may be of direct importance to the health of family members. Therefore, it is essential to analyze to what extent minors and/or parents can consent to NGS, and more specifically, to the return of incidental or secondary results. To date, a large part of the debate about the use of NGS in minors has concentrated on which results and secondary findings should (or should not) be returned.^{15–16} Although NGS is increasingly in use in the clinic, little attention has been paid to the specific consent issues with respect to minors.

The recent 2015 Position Statement on the ethical, legal and psychosocial implications of genetic testing in children and adolescents of the American Society of Human Genetics (ASHG) has described informed consent to genetic and genomic testing as a core principle for which there are few exceptions. They add that '[y]oung children lack decision-making capacity, so decisions about testing must be conducted through surrogates, usually the parents, and must be done with the child's best interest at heart' [our emphasis]. In light of this, our question is whether, and from what age, minors can provide lawful consent to health-care interventions and, consequently, NGS-related decisions. In this article, we aim to describe various existing legal approaches regarding the rights of minors to consent to health-care interventions. We then apply this to the context of NGS.

METHODOLOGY

To address this question, we described how laws in the 28 Member States of the European Union and Canada consider competent minors. The national legislations were identified by consulting websites of governmental agencies, and databases such as HumGen International, N-Lex and CanLII. If the legislation had no official English translation, an unofficial translation and analysis of the legal disposition were validated by local legal experts. We interrogated these documents using the following questions: What are the rights of minors to consent to health-care interventions, notably to NGS-related decisions? Can minors provide lawful consent and, if so, from what age?

In this paper, we define a minor as an individual who has not yet attained the age of legal majority under regional or national law and has not been declared emancipated. Emancipated minors are those who have achieved independence from their parents, through marriage, by entering military service or by court order. In a separate article, we have described the rights of minors to consent to living organ donation, and compared those with legislation addressing general health-care interventions.¹⁷

RESULTS

Our analysis demonstrates that there is little uniformity regarding the legal capacity to consent. The legislation on health-care decision-making varies between countries and often even between regions and provinces within those countries.

Capacity to consent presumed with legal majority

In general, adults are presumed to have the capacity to consent (although the presumption is rebuttable). Thus, when a minor reaches the legal age of majority, the capacity to consent is presumed. The age of majority is legally fixed and may vary according to domestic law

(see Table 1). The most commonly used age of majority is 18 years, such as in most parts of the European Union, as well as in various Canadian provinces (Alberta, Manitoba, Ontario, Prince Edward Island, Québec, Saskatchewan). However, some regions use alternative demarcations, such as 16 years (eg, Scotland) or 19 years (eg, the Canadian provinces of British Columbia, New Brunswick, Newfoundland and Labrador, Northwest Territories, Nova Scotia, Nunavut and Yukon Territory).

Competent minors and the capacity to consent to health-care decision

Legal frameworks adopt various approaches to determine the extent to which minors are legally capable to consent to health care and to make their own health-care decisions. These approaches are dictated by law or, when no statutory legislation exists, by common law. We identified three different approaches in the regions we studied: (i) consent by minors for health-care decisions from a fixed age onwards; (ii) competence assessment-based consent; and (iii) a mixed approach where fixed age limits are combined with competence-based approaches. Table 2 provides an overview of the different approaches to legal capacity in different regions. Supplementary Table 1 provides reference to the relevant legislations.

Legally fixed age for capacity to consent. Some laws state a fixed age at which an individual is considered capable of providing consent alone to medical care. This age usually differs from the legal age of majority. However, in some countries, such as France^{18,19} and Greece,²⁰ the age of legal capacity to consent to medical interventions usually coincides with the age of legal majority. Before that age, health-care interventions should take place with the consent of the parents and the assent of the minor should be sought, if he or she is capable of expressing his or her will and of participating in the decision.

When the fixed age of capacity to consent to medical care differs from the age of legal majority, it is often set at 16 years. For example, the Dutch law stipulates that 'a minor who has reached the age of 16 years is capable of entering into a treatment agreement for his own benefit, and to perform legal acts that are immediately related to the agreement.'²¹ Thus, under a legally fixed age approach, minors are presumed to be competent to give consent to medical treatment at the legally fixed age.

Some regions also use a fixed age approach, but with additional conditions or exceptions. This is the case in the province of Québec (Canada), where consent can be given directly by patients from 14 years onward. However, the person with parental authority or guardianship must be informed if the minor is required to remain in a health or social services establishment for more than 12 hours.²² In Bulgaria, dual consent to medical interventions is necessary when a minor is aged between 14 and 18 years. Thus, from such a minor, consent should be sought, together with the consent of the parent (or legal representative).²³ Dual consent is also required in Poland when the minor is more than 16 years old.²⁴ In Spain, where the age to consent to health-care is fixed at 16 years, consent shall nevertheless be provided by the legal representative if the minor is not intellectually or emotionally capable of understanding the scope of the intervention. However, the opinion of the minor will need to be taken into consideration from the age of 12 years onward.²⁵ The law also requires that if, according to the physician, the intervention entails a serious risk, the parents are to be informed and their opinion is to be taken into account.

Table 1 General approach regarding majority

<i>Legally fixed age</i>		<i>Legally fixed age (18 years)</i>	<i>Legally fixed age (19 years)</i>
<i>(< 18 years)</i>			
Canada		Alberta ^a , Manitoba ^b , Ontario ^c , Prince Edward Island ^d , Québec ^e , Saskatchewan ^f	British Columbia ^g , New Brunswick ^h , Newfoundland and Labrador ⁱ , Northwest Territories ^j , Nova Scotia ^k , Nunavut ^l , Yukon ^m
European Union	United Kingdom (Scotland) (16 years) ⁿ	Austria ^o , Belgium ^p , Bulgaria ^q , Croatia ^r , Czech Republic ^s , Cyprus ^t , Denmark ^u , Estonia ^v , Finland ^w , France ^x , Germany ^y , Greece ^z , Hungary ^{aa} , Italy ^{ab} , Latvia ^{ac} , Lithuania ^{ad} , Luxembourg ^{ae} , Netherlands ^{af} , Poland ^{ag} , Portugal ^{ah} , Romania ^{ai} , Slovakia ^{aj} , Slovenia ^{ak} , Spain ^{al} , Sweden ^{am} , United Kingdom (England & Wales) ^{an}	

^aCanada. Alberta. Age of Majority Act. s. 1. <https://www.canlii.org/en/ab/laws/stat/rsa-2000-c-a-6/latest/rsa-2000-c-a-6.html>. Accessed: August 2015.^bCanada. Manitoba. The Age of Majority Act. s. 1. <https://web2.gov.mb.ca/laws/statutes/ccsm/a007e.php>. Accessed: August 2015.^cCanada. Ontario. Age of Majority and Accountability Act. s. 1. <http://www.ontario.ca/laws/statute/90a07>. Accessed: August 2015.^dCanada. Prince Edward Island. Age of Majority Act. s. 1. <https://www.canlii.org/en/pe/laws/stat/rspei-1988-c-a-8/latest/rspei-1988-c-a-8.html>. Accessed: August 2015.^eCanada. Québec. Civil Code of Québec. s. 133. http://www2.publicationsduquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/CCQ_1991/CCQ1991_A.html. Accessed: August 2015.^fCanada. Saskatchewan. The Age of Majority Act. s. 2 (1). <http://www.publications.gov.sk.ca/details.cfm?p=393>. Accessed: August 2015.^gCanada. British Columbia. Infants Act. s. 17. <http://www.canlii.org/en/bc/laws/stat/rsbc-1996-c-223/latest/>. Accessed: August 2015.^hCanada. New Brunswick. Age of Majority Act. s. 1 (1). <https://www.canlii.org/en/nb/laws/stat/rsnb-2011-c-103/latest/rsnb-2011-c-103.html>. Accessed: August 2015.ⁱCanada. Newfoundland and Labrador. Age of Majority Act. s. 2 (a). <http://www.assembly.nl.ca/legislation/sr/annualstatutes/1995/A04-2.c95.htm>. Accessed: August 2015.^jCanada. Northwest Territories. Age of Majority Act. s. 2. <https://www.canlii.org/en/nt/laws/stat/rsnwt-1988-c-a-2/latest/rsnwt-1988-c-a-2.html>. Accessed: August 2015.^kCanada. Nova Scotia. Age of Majority Act. s. 2 (1). <http://nslegislature.ca/legc/statutes/agemajor.htm>. Accessed: August 2015.^lCanada. Nunavut. Age of Majority Act. s. 2. <https://www.canlii.org/en/nu/laws/stat/rsnwt-nu-1988-c-a-2/latest/rsnwt-nu-1988-c-a-2.html>. Accessed: August 2015.^mCanada. Yukon. Age of Majority Act. s. 1 (1). <http://www.gov.yk.ca/legislation/acts/agma.pdf>. Accessed: August 2015.ⁿUnited Kingdom. Scotland. Age of Legal Capacity (Scotland) Act 1991. s. 1 (1). <http://www.legislation.gov.uk/ukpga/1991/50/contents>. Accessed: August 2015.^oAustria. Civil Code (Allgemeines Bürgerliches Gesetzbuch). s. 21 (2). https://www.jusline.at/Allgemeines_Buergerliches_Gesetzbuch_%28ABGB%29_Langversion.html. Accessed: August 2015.^pBelgium. Civil Code (Burgerlijk Wetboek). s. 488. http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&a=N&table_name=wet&cn=1804032130. Accessed: August 2015.^qBulgaria. Act on Persons and Family (ЗАКОН ЗА ЛИЧНАТА И СЕМЕЙНАТА ПРАВА). s. 2. <http://lex.bg/bg/laws/doc/2121624577>. Accessed: August 2015.^rCroatia. Family Act (Obiteljski zakon). s. 117 (2). http://narodne-novine.nn.hr/clanci/sluzbeni/2014_06_75_1404.html. Accessed: August 2015.^sCzech Republic. Civil Code (občanský zákoník). s. 30 (1). <http://www.czechlegislation.com/en/89-2012-sb>. Accessed: August 2015.^tCyprus. Children Law (Ο Παιδιών Νόμος του). s. 2. <http://www.cylaw.org/nomoi/indexes/352.html>. Accessed: August 2015.^uDenmark. Act on Guardianship (Lov om værgemål). s. 8. <https://lovdata.no/dokument/NL/lov/2010-03-26-9>. Accessed: August 2015.^vEstonia. General Principles of the Civil Code Act (Tsiviilseadustiku üldosa seadus). s. 8 (2). <https://www.riigiteataja.ee/akt/106122010012>. Accessed: August 2015.^wFinland. Child Custody and Visiting Rights (Laki lapsen huollosta ja tapaamisoikeudesta). s. 3 (2). <https://www.finlex.fi/fi/laki/ajantasa/1983/19830361>. Accessed: August 2015.^xFrance. Civil Code (Code civil). s. 388. <http://www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006070721>. Accessed: August 2015.^yGermany. Civil Code (Bürgerliches Gesetzbuch). s. 2. http://www.gesetze-im-internet.de/englisch_bgb/englisch_bgb.html. Accessed: August 2015.^zGreece. Civil Code (Αστικός Κώδικας). s. 127. <http://www.ministryofjustice.gr/site/kodikis/%CE%95%CF%85%CF%81%CE%B5%CF%84%CE%AE%CF%81%CE%B9%CE%BF%91%CE%A3%CE%A4%CE%99%CE%9A%CE%9F%CE%A3%CE%9A%CE%A9%CE%94%CE%99%CE%9A%CE%91%CE%A3%tabid/225/language/el-GR/Default.aspx>. Accessed: August 2015.^{aa}Hungary. Civil Code (2013 évi V. törvény a Polgári Törvénykönyvről). s. 2:10 (1). http://njt.hu/cgi_bin/njt_doc.cgi?docid=159096. Accessed: August 2015.^{ab}Italy. Civil Code (Codice Civile). s. 2. <http://www.normattiva.it/uri-res/N2Ls?urn:nir:statuto:decreto.regio:1942-03-16;262vig>. Accessed: August 2015.^{ac}Latvia. Civil Code (Civillikums). s. 219. <http://likumi.lv/doc.php?id=90224>. Accessed: August 2015.^{ad}Lithuania. Civil Code (Lietuvos Respublikos civilinis kodeksas). s. 2.5 (1). http://www3.lrs.lt/pls/inter3/dokpaieska.showdoc?p_id=245495. Accessed: August 2015.^{ae}Luxembourg. Civil Code (Code Civil). s. 488. http://www.lexilux.public.lu/leg/textes/coordonnes/codes/code_civil/CodeCivil_PageAccueil.pdf. Accessed: August 2015.^{af}Netherlands. Civil Code (Burgerlijk Wetboek). s. 233. <http://www.wetboek-online.nl/wet/Burgerlijk%20Wetboek%20Boek%201.html>. Accessed: August 2015.^{ag}Poland. Civil Code (Kodeks cywilny). s. 10 (1). <http://isap.sejm.gov.pl/DetalsServlet?id=WDU19640160093>. Accessed: August 2015.^{ah}Portugal. Civil Code (Código Civil). s. 130. http://www.pgdlisboa.pt/leis/lei_mostra_articulado.php?nid=775&tabela=leis. Accessed: August 2015.^{ai}Romania. Law 287/2009 on the Civil Code (Legea 287/2009 privind Codul Civil). s. 38 (2). http://www.cdep.ro/pls/legis/legis_pck.htm_act?id=90254. Accessed: August 2015.^{aj}Slovakia. Civil Code (Občanský zákoník). s. 8 (2). <http://www.zakonypreludi.sk/z/1964-40>. Accessed: August 2015.^{ak}Slovenia. Law on Marriage and Family Relations (Zakon o zakonski zvezi in družinskih razmerjih). s. 117 (1). http://www.mdds.gov.si/fileadmin/mdds.gov.si/pageuploads/dokumenti__pdf/zakonodaja/law_on_marriage_and_family_relations.pdf. Accessed: August 2015.^{al}Spain. Civil Code [Código Civil]. s. 315. <http://www.boe.es/buscar/act.php?id=BOE-A-1889-4763>. Accessed: August 2015.^{am}Sweden. Parental Code (Föräldrabalk). s. 6 (2). http://www.riksdagen.se/sv/Dokument-Lagar/Lagar/Svenskforfattningssamling/Foraldrabalk-1949381_sfs-1949-381/. Accessed: August 2015.^{an}United Kingdom. England & Wales. Family Law Reform Act 1969. s. 1 (1). <http://www.legislation.gov.uk/ukpga/1969/46>. Accessed: August 2015.**Table 2** General approach towards capacity to consent of minors

<i>Legally fixed age for capacity to consent to medical interventions</i>		<i>Competence-based approach</i>	<i>Mixed approaches</i>
Canada	Newfoundland and Labrador, Quebec	Alberta, Nova Scotia, Northwest Territories, Nunavut, Saskatchewan, Ontario, Prince Edward Island, Yukon	British Columbia, Manitoba, New Brunswick
European Union	Bulgaria, Croatia, Cyprus, France, Greece, Hungary, Italy, Netherlands, Poland, Portugal, Slovakia, Spain, Sweden, United Kingdom (England & Wales)	Belgium, Czech Republic, Estonia, Finland, Germany, Luxembourg	Denmark, Latvia, Lithuania, Romania, Slovenia, United Kingdom (England & Wales)

Competence-based approaches. In certain countries, the law refers solely to a competence-based approach to evaluate the capacity of children to consent to medical interventions, regardless of their age. Rather than considering only the age of the child, the competence-based assessment considers the capacity of minors to make informed decisions through a case-by-case analysis of their cognitive and psychosocial maturity and their capacity to understand. Minors who

are considered to possess the same capacity as competent adults are thereby legally authorized to provide free and informed consent.

For example, in Canada, several provincial laws stipulate that minors can consent to their own medical care if they are deemed ‘capable’ of doing so (eg, Ontario,²⁶ Prince Edward Island,²⁷ Yukon²⁸). There is no set age when a child is deemed capable. The law generally considers them capable if they understand the need for the

medical treatment in question, what the treatment involves, and the benefits and risks if they receive – or do not receive – treatment. Various European countries, such as Belgium,²⁹ the Czech Republic,³⁰ Estonia,³¹ Finland³² and Luxembourg,³³ have adopted a similar system in which health-care professionals are responsible for evaluating the competence and maturity of a minor on a case-by-case basis.

In addition, when there is no statutory legislation addressing the capacity of minors to consent, a similar competence-based assessment approach is applied based on common law principles. According to common law, a minor who can understand and appreciate the nature and consequences of his or her decision and its alternatives is able to give valid consent, regardless of age. This is the case in three Canadian provinces (Alberta, Saskatchewan, Nova Scotia)³⁴ and in Scotland.³⁵ Courts are usually flexible in deciding if a child is capable, depending on how mature the child is and how grave the medical treatment. For example, a very young child may be able to consent to the dressing of a wound. On the other hand, an older child may not be deemed capable to refuse life-saving treatment. In this regard, it is worth mentioning that, in situations where a health-care intervention might not be in the child's best interests, that child's decision might be overruled. Similarly, a parent refusal may be overturned.

Mixed approaches. Some regions have adopted legislation combining a legally fixed age and an *ad hoc* maturity assessment of minors. For example, in Manitoba^{36,37} and New Brunswick³⁸ (Canada), a minor between 16 and 18 years has full 'legal' capacity and can make all health-care decisions, whereas to younger children, the competence-based approach applies. Nevertheless, some legislation places other limitations on recognition of the capacity of the minor to give consent. An example of this is in New Brunswick (Canada) where the law specifies that the consent of a minor who has not attained the age of 16 years to give medical treatment is (in the opinion of a legally qualified medical practitioner) as effective as if he had attained the age of majority under the following conditions: (i) the minor is capable of understanding the nature and consequences of a medical treatment; and (ii) the medical treatment and the procedure to be used are in the best interests and his continuing health and well-being of the minor.³⁸ The law of British Columbia (Canada) also specifies that the health-care provider should be satisfied that the minor understands the nature, consequences, benefits and risks of the health-care; and should have made reasonable efforts to determine and conclude that the health care is in the minor's best interests.³⁹

Similarly, in Latvia,⁴⁰ a minor patient from the age of 14 years can consent to medical treatment but, if the minor refuses to give his consent for medical treatment and according to the physician, the treatment is in the interests of this patient, the consent shall be given by the lawful representative of the minor patient.

DISCUSSION

Our analysis showed that there is considerable variation in the rights afforded to minors across countries and legislation. Although the age of legal majority is relatively standardized, countries adopt different approaches to determine the extent to which minors are capable of providing consent to health-care interventions and to make their own health-care decisions. These approaches are relevant when discussing decisions regarding the implementation of NGS in pediatric situations. When adult relatives of an affected individual are at risk of a disorder, both can decide for themselves whether or not to undergo a genetic test. However, in the case of at-risk incompetent minors, this decision will be made by others, most often the parents. As minors are not entitled to decide for themselves, all health-care decisions affecting

these minors should be addressed with particular caution. Thus, the 2015 ASHG Position Statement⁴¹ recognizes 'as children age, they gain decision-making capacity and experience with health conditions. Therefore, including children to various degrees as they age in genetic-and genomic- testing decisions and responses is important but challenging. [Also,] because children are young, decisions for them and by them might have implications for the course of their lives'.

Parents are morally and legally responsible for their children and are given authority to make decisions on their behalf, taking into consideration their best interests. This standard of 'best interests' has become a central component and a tool to guide ethical and legal discussions about children in the area of medicine, in both the literature^{42–44} and in national and international normative documents.^{45,46} In the context of genetic testing, there are many different views regarding what is in the child's best interests. This debate has arisen in discussions regarding predictive genetic testing and carrier testing in minors, particularly whether parents have the authority to request this testing for their children.^{47–48} On one hand,⁴⁹ some authors have suggested that parents are the most informed judges of what is in their child's best interests and that they should therefore be afforded the right and authority to decide for their children.⁵⁰ On the other hand, some have stressed that health-care professionals are not required to comply with parental requests. They argue that health-care professionals have a duty to promote the well-being of children and should override parental decisions that have significant potential to adversely impact the health or well-being of the child.⁵¹

A similar debate arose recently in response to the American College of Medical Genetics and Genomics (ACMG) guidelines⁵² regarding the duty to hunt for secondary variants outside the primary scope of an NGS analysis. The ACMG developed a list of 56 genes associated with 24 inherited conditions (with both early and late onset) that should be reported when a patient, regardless of age, undergoes NGS testing. The rationale for what has been called 'opportunistic screening' is based on the view that this could lead to medical benefit for the patient and their family. When testing is performed in children, the ACMG argues that identification of such pathogenic variants could benefit the child by providing important health information, enabling preventive or therapeutic interventions. In addition, this information could benefit the parents by informing them about potential heritable conditions within themselves before symptoms manifest. Hence, the ACMG considered 'that the ethical concerns about providing children with genetic risk information about adult-onset diseases were outweighed by the potential benefit to the future health of the child and the child's parent of discovering an incidental finding where intervention might be possible'.⁵² Furthermore, the ACMG considers it unethical for laboratories not to report such secondary variants, because it prevents parents from acting in their child's best interests and avoiding preventable harm.^{16,53} This obligatory 'duty to hunt' by genetic laboratories has received considerable criticism and authors have highlighted the lack of scientific evidence on which the selection of the ACMG's list of secondary variants is based, the potentially inappropriate and costly medical follow-up required if variants are classified as pathogenic, and the time and resources necessary to perform this 'opportunistic screening'.^{54,55} Although the original ACMG recommendations stated that analysis of these 56 genes should be mandatory, criticisms highlighting the importance of respecting patient autonomy and the patients' right not to know have led to an amendment in their policy, allowing parents to opt out from receiving those results for themselves and for their children.⁵⁴ Yet, parental decisions to receive or not receive these results may have different

outcomes for the child. As noted above, the ASHG adopted a more nuanced approach.⁴¹ They recognized that, although *in general* parents should be able to decline to receive secondary findings in advance of genetic testing, there are possible exceptions. Thus, where there is strong evidence that a secondary finding has urgent and serious implications for a child's health or welfare, and effective action can be taken to mitigate that threat, the ASHG recommends that the clinician communicates those findings to the parents or guardians, regardless of the general preferences stated by the parents.

In debates around the use of NGS in the pediatric population, insufficient attention has been paid to minors and their capacity, or not, to be involved in decisions around NGS. Our analysis of various legislation showed that many legal systems determine that minors are allowed, or may even be required, to make decisions about interventions such as NGS, based either on the fact that they have reached the age of legal majority or that they have sufficient capacity to make such decisions. It should be noted, however, that if the NGS tests in question are considered to be research, the legal framework surrounding the health care of minors may not apply. Indeed, NGS has resulted 'in a rapid evolution of research practices towards a process whereby suitable patients (usually with either cancer or a rare genetic disease) are referred by clinicians into genome sequencing research programs. However, rather than being driven mainly by a hypothesis-driven basic discovery motive, the goal is increasingly patient-focused and intended to find information of clinical benefit to the participant, indeed blurring the lines between 'patient' and 'research participant'.⁵⁶ As well explained by authors Lyon and Segal,⁵⁶ although this shift from the research setting to the clinic could have a positive impact for the patient, this changing landscape also begs for an in-depth discussion of the ethical and regulatory issues that face genomics research and genomic medicine.

In addition to the various legal approaches regarding the capacity of minors to consent and the different fixed age they are considered to be capable to give consent, the diversity is at least as great, if not more, when considering the capacity of minors to consent in a research context. Effectively, in their legal frameworks, some countries either do not differentiate between capacity to consent to health care or to research or are silent as to the required age (or criteria) of consent for participating in research, compared with others who do make this distinction (eg, Quebec (Canada)). Thus, in addition to the variety of approaches taken regarding the capacity to consent to health-care and the different fixed age or criteria to be considered 'capable', researchers also have to add to this puzzle the difficulty of establishing whether different rules apply or not with regards to the capacity to consent to research and, if so, which one. Indeed, some norms governing research will vary according to the level of risks associated with the research project. In a context where transnational and international research become more and more frequently the norm, such as in rare diseases research, this diversity of approaches presents significant difficulty for researchers in determining the capacity for minors to give consent. In practice, it could be challenging to identify the legal framework applicable or to have the appropriate policy for each country or jurisdiction.

Moreover, various laws emphasize that health-care professionals should not only involve children and adolescents who are legally capable to give consent to participate in the decision-making process, but should also encourage the involvement of all pediatric patients, regardless of whether they are considered legally competent. Indeed, the United Nations *Convention on the Rights of the Child* (1989) asserts that children have the right to express their views freely in all matters affecting them and to have their opinions taken into account (art. 12).

This supports that the growing levels of capacity to consent need to be taken seriously.

CONCLUSION

In the decision-making process and the consent procedures regarding the pediatric use of NGS, the opinion of minors should be taken into consideration as an increasingly determining factor in proportion to their age and degree of maturity. As we have demonstrated, certain minors do have the legal capacity to consent to the use of NGS and to make decisions about receiving incidental NGS results. Although they are often referred to as one single homogeneous population who always require parental consent, there are different categories of 'minors' and an amalgam of 'capacity': some minors are legally capable to consent to health-care decisions, some are capable to be involved in the decision-making process and others are legally capable or in some countries even required to participate in discussions and the decision-making process.

As we demonstrated, there are currently different categories of 'minors' and an amalgam of 'capacity', depending on the legal approach adopted by regional or local legislations. In addition, this amalgam becomes even greater when we extend the breach to take into account the specific rules that govern the research context. As genomic sequencing of children for health-care purposes and research often become intertwined activities,⁵⁷ relevant normative frameworks, including consent to health-care and research, as well as the return of NGS results, need to be carefully and critically analyzed and, if necessary, adapted to the contemporary situation (ie, blurred line between clinical and research context). Also, the need for international research collaborations (eg, for rare diseases research or pediatric cancer) call for a harmonization of the norms.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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- 1 van EL, Cornel MC, Borry P et al: Whole-genome sequencing in health care: recommendation of the European Society of Human Genetics. *Eur J Hum Genet* 2013; **21**: 580–584.
- 2 Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE: Rare-disease genetics in the era of next-generation sequencing: discovery to translation. *Nat Rev Genet* 2013; **14**: 681–691.
- 3 Vrijenhoek T, Kraaijeveld K, Elferink M et al: Next-generation sequencing-based genome diagnostics across clinical genetics center: implementation choices and their effects. *Eur J Hum Genet* 2015; **23**: 1142–1150.
- 4 Castéra L, Krieger S, Rousselin A et al: Next-generation sequencing for the diagnosis of hereditary breast and ovarian cancer using genomic capture targeting multiple candidate genes. *Eur J Hum Genet* 2014; **22**: 1305–1313.
- 5 Dodge JA, Chigladze T, Donadieu J et al: The importance of rare diseases: from the gene to society. *Arch Dis Child* 2011; **96**: 791–792.

- 6 Solomon BD, Hadley DW, Pineda-Alvarez DE *et al*: Incidental medical information in whole-exome sequencing. *Pediatrics* 2012; **129**: e1605–e1611.
- 7 Saunders CJ, Miller NA, Soden SE *et al*: Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. *Sci Transl Med* 2012; **4**: 154ra135.
- 8 Graubert T, Stone R: AML genomics for the clinician. *Semin Hematol* 2014; **51**: 322–329.
- 9 Biesecker LG, Biesecker BB: An approach to pediatric exome and genome sequencing. *Curr Opin Pediatr* 2014; **26**: 639–645.
- 10 Feero WG, Guttmacher AE: Genomics, personalized medicine, and pediatrics. *Acad Pediatr* 2014; **14**: 14–22.
- 11 Amendola LM, Dorschner MO, Robertson PD *et al*: Actionable exomic incidental findings in 6503 participants: challenges of variant classification. *Genome Res* 2015; **25**: 305–315.
- 12 Dorschner MO, Amendola LM, Turner EH *et al*: Actionable, pathogenic in 1,000 participants' exomes. *Am J Hum Genet* 2013; **93**: 631–640.
- 13 Jang MA, Lee SH, Kim N, Ki CS: Frequency and spectrum of actionable pathogenic secondary findings in 196 Korean exomes. *Genet Med* 2015; **17**: 1007–1011.
- 14 Johnston JJ, Rubinstein WS, Facio FM *et al*: Secondary variants in individual undergoing exome sequencing: screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. *Am J Hum Genet* 2012; **91**: 97–108.
- 15 Green RC, Lupski JR, Biesecker LG: Reporting genomic sequencing results to ordering clinicians: incidental, but not exceptional. *JAMA* 2013; **310**: 365–366.
- 16 McGuire AL, Joffe S, Koenig BA *et al*: Point-counterpoint. Ethics and genomic incidental findings. *Science* 2013; **340**: 1047–1048.
- 17 Thys K, Van Assche K, Nys H *et al*: Living organ donation by minors: an analysis of the regulations in EU member states. *Am J Transplant* 2016; e-pub ahead of print 12 May 2016; doi:10.1111/ajt.13868.
- 18 France. Code of Public Health (Code de la santé publique). s. L-1111-4 & R-4127-42. Available at <http://legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006072665>. Accessed August 2015.
- 19 France. Civil Code (Code civil). s. L371-1. Available at <http://www.legifrance.gouv.fr/affichCode.do?cidTexte=LEGITEXT000006070721>. Accessed August 2015.
- 20 Greece. Law 3418/2005 Code of Medical Ethics (Κώδικας Ιατρικής Δεοντολογίας). Available at <http://www.isth.gr/images/uploads/J1E7IM6.pdf>. Accessed August 2015.
- 21 Netherlands. Medical Treatment Agreement Act (Wet op de Geneeskundige Behandelingsovereenkomst). s. 447 (1). Available at <https://www.dwanginzorg.nl/rechten/wetten/wgbo>. Accessed August 2015.
- 22 Canada. Quebec. Civil Code of Québec. s. 14. Available at http://www2.publications-duquebec.gouv.qc.ca/dynamicSearch/telecharge.php?type=2&file=/CCQ_1991/CCQ1991_A.html. Accessed August 2015.
- 23 Bulgaria. Health Act (Закон за здравето). Available at www.customs.bg/document/3233. Accessed August 2015.
- 24 Poland. Act of 5 December 1996 on professions of doctor and dentist (Ustawa z dnia 5 grudnia 1996 r. o zawodach lekarza i lekarza dentysty). s. 32 (2) & 32 (5). Available at http://www.oil.org.pl/xml/oil/oil68/tematy/lek_lek_dent. Accessed August 2015.
- 25 Spain. Act 41/2002 of November 14, 2002 on the autonomy of the patient and on the rights and obligations in matter of clinical information and documentation (Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica). Available at <http://www.boe.es/buscar/doc.php?id=BOE-A-2002-22188>. Accessed August 2015.
- 26 Canada. Ontario. Health Care Consent Act. s. 4 (1) & 10 (1). Available at <http://www.ontario.ca/laws/statute/96h02>. Accessed August 2015.
- 27 Canada. Prince Edward Island. Consent to Treatment and Healthcare Directives Act. Available at <http://www.canlii.org/en/pe/laws/stat/rspei-1988-c-c-17.2/latest/rspei-1988-c-c-17.2.html>. Accessed August 2015.
- 28 Canada. Yukon. Care Consent Act. Available at http://www.gov.yk.ca/legislation/acts/care_consent_c.pdf. Accessed August 2015.
- 29 Belgium. Law on the Rights of Patients (Loi relative aux droits du patient). s. 12 (1) & 12 (2). Available at <http://www.ejustice.just.fgov.be/loi/loi.htm>. Accessed August 2015.
- 30 Czech Republic. Civil Code (Občanský zákoník). s. 31. Available at <http://www.czechlegislation.com/en/89-2012-sb>. Accessed August 2015.
- 31 Estonia. Law of Obligations Act (Võlaõigusseadus). s. 766 (4). Available at <https://www.riigiteataja.ee/en/eli/506112013011/consolide>. Accessed August 2015.
- 32 Finland. Act on the Status and Rights of Patients (Laki potilaan asemasta ja oikeuksista). s. 7. Available at <http://www.finlex.fi/en/laki/kaannokset/1992/en19920785.pdf>. Accessed August 2015.
- 33 Luxembourg. Law of 24 July 2014 on the rights and obligations of the patient (Loi du 24 juillet 2014 relatives aux droits et obligations du patient). s. 13 (2). Available at <http://eli.legilux.public.lu/eli/etat/leg/loi/2014/07/24/n2>. Accessed August 2015.
- 34 AC v Manitoba (Director of Child and Family Services), 2009 SCC 30.
- 35 Gillick v. West Norfolk and Wisbech Area Health Authority, [1986] AC 112 House of Lords.
- 36 Canada. Manitoba. Health Care Directives Act. Available at <https://web2.gov.mb.ca/laws/statutes/ccsm/h027e.php>. Accessed August 2015.
- 37 C. v. Wren, (1987) 35 D.L.R. (4) 419.
- 38 Canada. New Brunswick. Medical Consent of Minors Act. s. 2 and 3 (1). Available at <https://www.canlii.org/en/nb/laws/stat/snb-1976-c-m-6.1/latest/snb-1976-c-m-6.1.html>. Accessed August 2015.
- 39 Canada. British Columbia. Infants Act. s. 17. Available at http://www.bclaws.ca/Recon/document/ID/freeside/00_96223_01. Accessed August 2015.
- 40 Latvia. Civil Code (Civiltikums). s. 219. Available at <http://likumi.lv/doc.php?id=90224>. Accessed August 2015.
- 41 Botkin JR, Belmont JW, Berg JS *et al*: Points to consider: ethical, legal and psychosocial implications of genetic testing in children and adolescents. *Am J Hum Genet* 2015; **97**: 6–21.
- 42 Kopelman LM: Using the Best Interests Standard to decide whether to test children for untreatable, late-onset genetic diseases. *J Med Philos* 2007; **32**: 375–394.
- 43 Geelen E, Van Hoyweghen I, Doevendans PA, Marcelis CL, Horstman K: Constructing 'best interests': genetic testing of children in families with hypertrophic cardiomyopathy. *Am J Med Genet A* 2011; **155A**: 1930–1938.
- 44 Pelias MK: Genetic testing of children for adult-onset diseases: is testing in the child's best interests? *Mt Sinai J Med* 2006; **73**: 605–608.
- 45 United Nations Educational, Scientific and Cultural Organization. Universal Declaration on the Human Genome and Human Rights. Available at <http://www.unesco.org/new/en/social-and-human-sciences/themes/bioethics/human-genome-and-human-rights/>. Accessed August 2015.
- 46 European Union. Charter of Fundamental Rights of the European Union. Available at <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:12012P/TXT>. Accessed August 2015.
- 47 Duncan RE, Gillam L, Savulescu J, Williamson R, Rogers JG, Delatycki MB: Reply to Richards: 'Predictive genetic testing of adolescents for Huntington disease: a question of autonomy and harm'. *Am J Med Genet A* 2008; **146A**: 2447–2448.
- 48 Clayton EW, McCullough LB, Biesecker LG *et al*: Addressing the ethical challenges in genetic testing and sequencing of children. *Am J Bioeth* 2014; **14**: 3–9.
- 49 Borry P, Goffin T, Nys H, Dierickx K: Attitudes regarding carrier testing in incompetent children: a survey of European clinical geneticists. *Eur J Hum Genet* 2007; **15**: 1211–1217.
- 50 Rhodes R: Why test children for adult-onset genetic diseases? *Mt Sinai J Med* 2006; **73**: 609–616.
- 51 Borry P, Goffin T, Nys H, Dierickx K: Predictive genetic testing in minors for adult-onset genetic diseases. *Mt Sinai J Med* 2008; **75**: 287–296.
- 52 Green RC, Berg JS, Grody WW *et al*: ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med* 2013; **15**: 565–574.
- 53 American College of Medical Genetics and Genomics: Incidental findings in clinical genomics: a clarification. *Genet Med* 2013; **15**: 664–666.
- 54 Ross LF, Rothstein MA, Clayton EW: Mandatory extended searches in all genome sequencing: 'incidental findings', patient autonomy, and shared decision making. *JAMA* 2013; **310**: 367–368.
- 55 Burke W, Antommaria AH, Bennett R *et al*: Recommendations for returning genomic incidental findings? We need to talk!. *Genet Med* 2013; **15**: 854–859.
- 56 Lyon GJ, Segal JP: Practical, ethical and regulatory considerations for the evolving medical and research genomics landscape. *Applied & Translational Genomics* 2013; **2**: 34–40.
- 57 Van El CG, Cornel MC, Borry P *et al*: Whole-genome sequencing in health care—Recommendations of the European Society of Human Genetics. *Eur J Hum Genet* 2013; **21**: 580–584.



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